PATENT SPECIFICATION (11) 1401579

1401579

(21) Application No. 42044/73 (22) Filed 6 Sept. 1973

(31) Convention Application No. RI 485 (32) Filed 6 Sept. 1972 in

(33) Hungary (HU)

(44) Complete Specification published 30 July 1975

(51) INT CL² C07D 401/14//C07C 59/12 C07D 209/14 309/30

(52) Index at acceptance

C2C 1343 136X 1672 20Y 213 214 215 237 246 247 250 252 253 25Y 282 29X 29Y 305 30Y 342 34Y 351 352 360 361 367 36Y 37X 386 43X 601 623 625 62X 638 652 66Y 761 767 776 CT KQ ZF

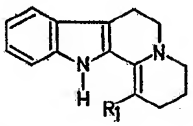
(72) Inventors CSABA SZANTAY, LAJOS SZABO
GYORGY KALAUS, JANOS KREIDL
BELA STEFKO, TIBOR KEVE
ISTVAN POLGAR and PETER TURCSANYI

(54) INDOLO-QUINOLIZINES

(71) We, RICHTER GEDEON VEGYESZETI GYAR RT., a Hungarian body corporate of 21 Gyomroi ut, Budapest X, Hungary, do hereby declare the invention for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

This invention relates to indolo[2,3-a]-quinolizines and a process for their preparation.

According to one feature of the present invention there are provided compounds of general formula (I)



(I)

wherein R_1 represents a methyl group or an alkyl group containing from 3 to 10 carbon atoms and the acid addition salts thereof.

These alkyl derivatives are novel compounds and are useful intermediates in the production of pharmaceutically active compounds.

The compound of the above formula (I) wherein R_1 represents an ethyl group is a known substance and is used as starting material for the total synthesis of vincamine.

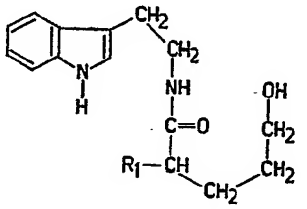
According to a known process for the preparation of 1 - ethyl - 1,2,3,4,6,7 - hexahydro - 12H - indolo[2,3 - a]quinolizine (E. Wenckert, B. Wickberg: J. Am Chem Soc. 87, 1580/1965/) diethyl ethyl - γ - bromo - propyl - manolate (easily obtained from malonic ester) is hydrolysed and decarboxylated by boiling with hydrobromic acid. The obtained compound is esterified with diazomethane. The thus-formed methyl 2 - ethyl - 5 - bromovalerate is condensed with tryptamine, and the obtained 1 - (3 - indolyl - ethyl) - 3 - ethyl - piperidone - 2 is treated with phosphorus oxychloride to yield the desired product.

This known process has, however, several disadvantages, among which the following are to be mentioned: the product is obtained in a relatively low yield; the reaction of tryptamine and methyl 2 - ethyl - 5 - bromovalerate requires a very long time of boiling at 70°C, which involves the decomposition of the heat-sensitive indole compound and comsequently decreases the yield; the esterification of 2 - ethyl - 5 - bromo - valeric acid requires particularly severe conditions, such as treatment with diazomethane, presumably due to the blocking effect of the tertiary carbon atom adjacent to the carboxyl group; moreover the hydrolysis with hydrogen bromide is a highly corrosive operation requiring particular care and structural materials of special quality. All these disadvantages render the above process unsuitable for large-scale realization.

According to another known process (A. LeHir, M. Janot, D. Stolk: Bull. Soc. Chim. France, 551/1958/), β-acetyl-pyridine is reacted with tryptophylic bromide. The obtained salt is treated with an acid to yield 1 - acetyl - 1,2,3,4,5,6,7,12b - octahydro - indole[2,3 - a]quinolizine. The acetyl group of this compound is reduced to an ethyl group, and this latter compound is subjected to oxidation in the presence of mercuric acetate to yield the desired product. The process has the disadvantage that the starting materials are not easily available, the product is obtained with a relatively low yield, and the reduction of the keto group as well as the oxidation with mercuric acetate cannot be realized on an industrial scale without difficulties.

According to a further feature of the pre-

sent invention there is provided a process for the preparation of the indolo[2,3 - a]-quinolizines of general formula (I) and their salts, wherein R_1 is as hereinbefore defined, which comprises reacting an indole derivative of general formula (II),

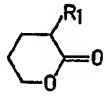


(II)

wherein R_1 is as herein before defined, with a water-labile, phosphorus compound selected from a halide, an oxide and an oxyhalide of phosphorus, at temperatures of from 50 to 250°C, and subsequently with a base, and if desired, the thus-obtained free base is converted into its acid addition salt.

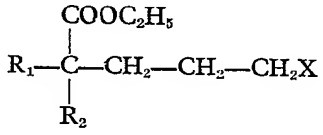
This process can easily be realised on an industrial scale and is advantageous in that it provides high yields and can be used for the preparations of any 1,2,3,4,6,7 - hexahydroindolo - [2,3 - a]quinolizine having an alkyl group of medium chain length in position 1.

The indole derivatives of general formula II may be prepared by reacting tryptamine with a compound of formula (III),



(III)

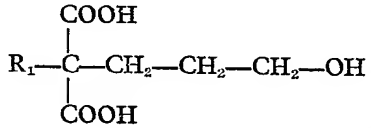
wherein R_1 is as defined above, optionally in the presenece of a solvent. The compounds of general formula (III) may be obtained by heating a compound of formula (V),



(V)

wherein R_1 is as defined above, R_2 is a cyano or ethoxy-carbonyl group and X is a halogen, with a base in the presence of water, followed by acidification and maintenance at elevated temperature, optionally in the presence of solvent.

The compound of formula (V) may also be used to prepare a compound of formula (IV),



(IV)

wherein R_1 is as defined above, by reaction with a base in the presence of water, followed by acidification. The compound of formula (IV) may be reacted in the molten state with tryptamine to yield a compound of formula (II).

The starting compounds of general formula (V) can be prepared as described in the literature.

The above-described syntheses of the compounds of formula (I) can be started with any of the intermediates; in such instances only the subsequent steps are to be carried out.

According to one method of the invention the intermediates are isolated and all the reaction steps are started with these isolated compounds. In some instances the isolation of the intermediates is, however, not necessary, and they can be used for the subsequent step directly in the reaction mixture where they were formed. Under such conditions it is sometimes advisable to change the solvent or reaction medium for another solvent or medium prior to the subsequent reaction step.

In the process according to the invention, the indole derivative of formula (II) is preferably dissolved or suspended in an organic solvent before reaction, at a temperature of from 50 to 250°C, with the phosphorus compound. The most advantageous temperature range for the reaction is 110 to 160°C. Preferred organic solvents are aromatic or aliphatic hydrocarbons, optionally halogenated, for example benzene, toluene, xylene, chloroform, carbon tetrachloride, dichloroethane, trichloromethane, tetrachloroethane or chlorobenzene. When a liquid, the phosphorus compound may be used in excess so as to serve simultaneously as the reaction medium.

The water-labile halide, oxide or oxyhalide of phosphorous is preferably used in the presence of a halogen or hydrogen halide. Among these reagents phosphorus pentachloride, phosphorus trichloride, phosphorus oxychloride, a mixture of phosphorus pentoxide and hydrochloric acid, and a mixture of phosphorus trioxide and bromine are most preferred. The phosphorus compound can be used in an amount equivalent with the indole derivative, but it is preferred to add an excess of the phosphorus compound to the reaction mixture. In this latter case the excess phosphorus compound is removed after the reaction e.g. by boiling the mixture with water or alcohol.

When the reaction with the phosphorus compound terminates, a base is added to the mixture, and the reaction mixture is maintained at room temperature or at elevated temperatures, preferably at 30 to 80°C, or at the boiling point of the mixture. The thus-obtained base of the general formula (I) is optionally isolated from the mixture, or the mixture can be used as such in further reac-

Example 4

A) Butyl - γ - hydroxy - propyl - malonic acid

A mixture of 28.6 g. of ethyl butyl - γ - chloro - propyl - malonate (n_D^{25}=1.4465), 14 g. (0.35 moles) of sodium hydroxide, 30 ml. of water and 50 ml. of alcohol is refluxed with stirring for 2 hours and thereafter the alcohol is distilled off. The residue is cooled to 0°C and acidified to pH 1 with concentrated hydrochloric acid. The separated crystals are filtered off, washed with water and dried. 17.2 g. (79%) of butyl - γ - hydroxy - propyl - malonic acid are obtained, m.p.: 137—138°C (at a heating rate of 4°C/min.).

Analysis:
Calculated for $C_{10}H_{18}O_5$ (M=218.1):
C: 55.05% H: 8.26%
Found: C: 54.81% H: 8.05%
IR spectrum: $\nu_{max.}$ 1700 and 1725 cm^{-1} (acid C=O).

B) 3 - butyl - tetrahydro - 2H - pyran - 2 - one

A mixture of 21.8 g. (0.1 moles) of butyl - γ - hydroxy - propyl malonic acid and 150 ml. of chlorobenzene is refluxed for 0.5 hours and thereafter 50 ml. of the solvent are distilled off under atmospheric pressure. The residue is subjected to fractional distillation in vacuo, and the product is collected at 126—134°C/5 mmHg. 13.3 g. (85%) of 3 - butyl - tetrahydro - 2H - pyran - 2 - one are obtained; b.p.: 104—106°C/0.7 mmHg., n_D^{25}=1.4498.

Analysis:
Calculated for $C_9H_{16}O_2$ (M=156.22):
C: 69.19% H: 10.32%
Found: C: 68.86% H: 9.95%
IR spectrum (film): $\nu_{max.}$ 1730 cm^{-1} (ester C=O).
NMR spectrum (CCl_4): τ=5.78 (2H, ester —C*H*$_2$—), 7.38—8.90 (11H, —C*H*$_2$—, —C*H*=), 9.08 (3H, —C*H*$_3$).

C) 3 - [N - (2 - butyl - 5 - hydroxy - valeroyl) - 2 - aminoethyl] - indole

A mixture of 18.7 g. (0.12 moles) of 3 - butyl - tetrahydro - 2H - pyran - 2 - one, 16 g. (0.1 moles) of tryptamine and 150 ml. of chlorobenzene is refluxed for 4 hours under nitrogen. The reaction mixture is cooled and the separated crystals are filtered off, washed and dried. 30.3 g. (96%, calculated for the tryptamine) of 3 - [N - (2 - butyl - 5 - hydroxy - valeroyl) - 2 - amino - ethyl] - indole are obtained; m.p.: 78—80°C (at a heating rate of 4°C/min.).

Analysis:
Calculated for $C_{19}H_{28}N_2O_2$ (M=316.43):
C: 72.11% H: 8.92% N: 8.85%
Found: C: 71.80% H: 9.18% N: 8.92%
IR spectrum (KBr): $\nu_{max.}$ 3250 cm^{-1} (indole NH), 1622 cm^{-1} (amide (C=O).

D) 1 - Butyl - 1,2,3,4,6,7 - hexahydro - indolo[2,3 - a] - quinolizinium per - chlorate

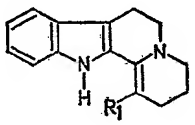
A mixture of 316.4 g. of 3 - [N - (2 - butyl - 5 - hydroxy - valeroyl) - 2 - amino - ethyl] - indole. 300 ml. of chlorobenzene and 350 ml. of phosphorus oxychloride is refluxed for 3 hours and thereafter 100 ml. of water and 400 ml. of dichloroethane are added to the mixture. The mixture is cooled to 20°C, and the phases are separated from each other. 100 ml. of water and 300 ml. of dichloroethane are added to the organic phase, and the pH of the mixture is adjusted to 11 to 14 with aqueous sodium hydroxide solution. The mixture is stirred for 2 hours at 60°C and thereafter it is processed as described in Example 1/C.

34.6 g. (91%) of 1 - butyl - 1,2,3,4,6,7 - hexahydro - indolo[2,3 - a]quinolizinium perchlorate are obtained; m.p.: 201—202°C (at a heating rate of 4°C/min.).

Analysis:
Calculated for $C_{19}H_{25}N_2O_4Cl$ (M=380.86):
C: 59.91% H: 6.61% N: 7.35%
Found: C: 60.26% H: 6.72% N: 7.03%
IR spectrum (KBr): $\nu_{max.}$ 3240 cm^{-1} (indole —NH), 1622 cm^{-1} ($C=\overset{+}{N}=$).
UV spectrum: $\lambda_{max.}$ 359 nm., log. ε=4.3598.

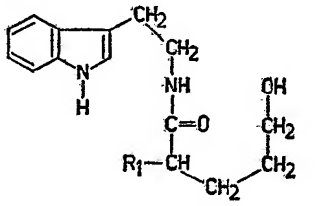
WHAT WE CLAIM IS:—

1. A process for the preparation of indolo-[2,3-a]quinolizines of general formula (I),



(I)

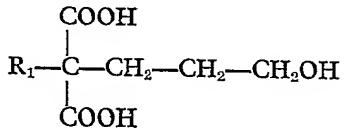
or of acid-addition salts thereof, wherein R_1 represents an alkyl group containing from 1 to 10 carbon atoms, in which an indole derivative of formula (II),



(II)

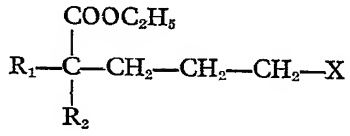
wherein R_1 has the same meanings as defined above, is reacted with a water-labile phosphorus compound selected from a halide, an oxide and an oxyhalide of phosphorus, at a temperature of from 50 to 250°C, and subsequently with a base, and, if desired, the thus, obtained free base is converted into its acid addition salt.

2. A process as claimed in claim 1 wherein the compound of formula (II) is prepared by reacting a compound of formula (IV),



wherein R_1 is as defined in claim 1, with tryptamine in the molten state.

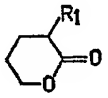
3. A process as claimed in claim 2 in which the compound of formula (IV) is prepared by reacting a compound of formula (V),



(V)

wherein R_1 is as defined in claim 1, R_2 represents a cyano or ethoxycarbonyl group and X represents a halogen atom, with a base in the presence of water, followed by acidification.

4. A process as claimed in claim 1 wherein the compound of formula (II) is prepared by reacting a compound of formula (III),



(III)

wherein R_1 is as defined in claim 1, with tryptamine, optionally in the presence of a solvent.

5. A process as claimed in claim 4 wherein the compound of formula (III) is prepared by reacting a compound of formula (V) with a base in the presence of water, followed by acidification and maintenance at elevated temperature, optionally in the presence of a solvent.

6. A process as claimed in any of claims 1 to 5, in which the starting compounds or intermediates are used directly in the reaction mixture where they are formed, without any isolation step.

7. A process as claimed in any of claims 1 to 6, in which the phosphorus compound is phosphorus pentachloride, phosphorus trichloride or phosphorus oxychloride.

8. A process as claimed in any of claims 1 to 7, in which an oxygenated phosphorus compound is used in the presence of a halogen or hydrohalic acid.

9. A process as claimed in any of claims 1 to 8, in which the reaction with the phosphorus compound is carried out in the presence of an organic solvent.

10. A process as claimed in claim 9 in which the organic solvent comprises an aromatic or aliphatic hydrocarbon, optionally halogenated.

11. A process as claimed in claim 10 in which the organic solvent is benzene, toluene, xylene, trichloromethane, dichloroethane, chloroform, carbon tetrachloride, chlorobenzene or tetrachloroethane.

12. A process as claimed in any of claims 1 to 11 wherein reaction is carried out at 110 to 160°C.

13. A process as claimed in any of claims 1 to 12, in which the reaction with the phosphorus compound is carried out in the presence of an excess of the phosphorus compound.

14. A process as claimed in any of claims 1 to 13, in which phosphorus oxychloride is used as the phosphorus compound.

15. A process as claimed in claim 14 wherein the reaction with the phosphorus compound is carried out at the boiling point of the reaction mixture.

16. A process as claimed in any of claims 1 to 15, in which an alkali metal or alkaline earth metal hydroxide or an alkali metal salt furnishing alkaline hydrolysis products is used as base.

17. A process as claimed in any of claims 1 to 16 in which the reaction with a base is carried out at room temperature or at an elevated temperature.

18. A process as claimed in claim 17 in which the reaction is carried out at 30 to 80°C.

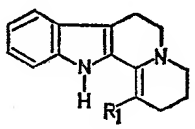
19. A process as claimed in any of claims 1 to 18, in which the reaction with a base is carried out in aqueous medium, in the presence of a water-immiscible organic solvent.

20. A process as claimed in claim 19 wherein the organic solvent is chloroform, dichloroethane, dichloromethane or chlorobenzene.

21. A process as claimed in claim 1 substantially as hereinbefore described.

22. A process as claimed in claim 1 substantially as hereinbefore described with reference to the Examples.

23. Compounds of general formula (I)



(I)

wherein R_1 represents a methyl group or an alkyl group containing from 3 to 10 carbon atoms and the acid addition salts thereof.

24. 1 - Butyl - 1,2,3,4,6,7 - hexahydro - indolo[2,3 - a]quinolizine and acid-addition salts thereof.

25. Compounds as claimed in claim 23

other than those claimed in claim 24 substantially as herein described.

26. Compounds as defined in claim 1 whenever prepared by a process as claimed in any of claims 1 to 22.

For Applicants of
FRANK B. DEHN
Imperial House,
15—19 Kingsway,
London WC2D 6UZ

Printed for Her Majesty's Stationery Office, by the Courier Press, Leamington Spa, 1975.
Published by The Patent Office, 25 Southampton Buildings, London, WC2A 1AY, from which copies may be obtained.